

B1 concluded  
terminus of C5a (SEQ. ID NO:1, C5a<sub>65-74</sub>, ISHKDMQLGR) twice with I<sub>65</sub>Y and H<sub>67</sub>F (eg. 2) led to enhancement of agonist potency by about 2 orders of magnitude. These results are summarised in Table 2. Analyses of Ramachandran plots and 2D NMR spectra for compound 2 suggested that certain structural features, namely a twisted "helix-like" backbone conformation for residues 65-69 and a  $\beta$ -turn for residues 71-74, might be responsible for activity. These preliminary results provided some insight to structural requirements for tight binding to a C5a receptor.--

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Pages 30 and 37, please replace Tables 2 and 4 as shown on the attached pages:

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--Table 2  
Pharmacological Activity of C5a Agonist Analogues\*

Peptide No.	Peptide	Fetal Artery EC <sub>50</sub> (μM)	PMN Enzyme Release EC <sub>50</sub> (μM)	Binding Affinity IC <sub>50</sub> (μM)
SEQ. ID NO:1	C5a <sub>65-74</sub> (ISHKDMQLGR)	>1000	>1000	>1000
SEQ. ID NO:2	YSFKDMQLGR	9.6	92	1.3
SEQ. ID NO:3	YSFKDMPLaR	0.5	72	3.7
SEQ. ID NO:4	YSFKPMPLaR	0.2	4.1	6.0
SEQ. ID NO:5	C5a <sub>37-46</sub> -ahxYSFKPMPLaR	0.06	5.9	0.7
SEQ. ID NO:6	C5a <sub>12-20</sub> -ahxYSFKPMPLaR	0.08	0.7	0.07
	C5a	0.02	0.03	0.0006

\*Finch *et al*, 1997

Table 4  
Receptor-Binding Affinities<sup>a</sup> and Antagonist Activities<sup>b</sup> in Human PMNs

Compound	Receptor Affinity <sup>a</sup> IC <sub>50</sub> (μM)	Antagonist Potency <sup>b</sup> IC <sub>50</sub> (μM)	Agonist Activity <sup>c</sup>
SEQ. ID NO:7 MeFKP (dCha)Wr	1.8 (15)	0.085 (9)	No
SEQ. ID NO:8 MeFKP (dCha)Wr-CONH <sub>2</sub>	14 (5)	0.5 (3)	No
SEQ. ID NO:9 MeFKP (dCha)WR	11 (5)	0.7 (3)	No
SEQ. ID NO:10 MeFKPLWR	144 (1)	>1000 (3)	nd
SEQ. ID NO:11 Ac-F-[KP (dCha)Wr]	3.2 (40)	0.090 (5)	No
SEQ. ID NO:12 Ac-F-[OP (dCha)Wr]	0.28 (6)	0.012 (4)	No
SEQ. ID NO:4 YSFKPMPLaR	6.0 <sup>d</sup>	-	Yes
SEQ. ID NO:1 C5a <sub>65-74</sub> , ISHKDMLGR	>1000 <sup>e</sup>	-	-
C5a	0.0008 (9)	-	Yes

Number of experiments in parenthesis. Corrected for amino acid content

Square brackets indicate cyclic portion.

nd= not determined

<sup>a</sup> 50% reduction in binding of <sup>125</sup>I-C5a to intact human PMNs

<sup>b</sup> 50% reduction in myeloperoxidase secretion from human PMNs mediated by 100 nM C5a

<sup>c</sup> Agonist activity in dose range 0.1 nM-1 nM

<sup>d</sup> Finch *et al*, 1997; <sup>e</sup> Kawai *et al*, 1991

Page 39, please replace the text beginning at line 6 through the end of the page as follows:

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Compound	n	R	Isomer*	Receptor Affinity $\mu\text{M}$	Agonist Activity
SEQ. ID NO:13	1	H	S-	9	No
SEQ. ID NO:14			R-	34	No
SEQ. ID NO:15	2	H	S-	0.3	No
SEQ. ID NO:16			R-	3.7	No
SEQ. ID NO:17	3	Ac	S-	0.3	No
SEQ. ID NO:11		Ac	R-	38	No
SEQ. ID NO:18	4	Ac	S-	3.2	No
SEQ. ID NO:12		Ac	R-	51	No

Refers to stereochemistry of Arg side chain

Pages 41 and 42, please replace Table 6 as shown on the attached page:

AS D<sub>2</sub> Me

--Table 6

Effect of Cyclisation on Antagonist Binding Affinity and Antagonist Potency

PEPTIDE		pD <sub>2</sub> ± SE <sup>a</sup>	IC <sub>50</sub> (μM) <sup>a</sup>	(n)	pD <sub>2</sub> ± SE <sup>b</sup>	IC <sub>50</sub> (μM) <sup>b</sup>	(n)
SEQ. ID NO:11	AcF-[KpdChaWR]	5.49 ± 0.22	3.2	4	7.07 ± 0.29	0.09	5
SEQ. ID NO:18	AcF-[OPdChaWR]	6.44 ± 0.14*	0.4	9	7.30 ± 0.09	0.05	9
SEQ. ID NO:19	[FWPdChaWR]	4.37 ± 0.36*	43	3	nd		
SEQ. ID NO:20	AcF-[KmdChaWR]	4.81 ± 0.06	15	2	nd		
SEQ. ID NO:21	AcF-[KKdChaWR]	3.94 ± 0.4	116	3	4.88	13	1

Effect of length of linker in cycle on antagonist binding affinity and antagonist potency

SEQ ID NO:22	AcF-[XPdChaWR]	5.02 ± 0.07	9.5	3	4.71 ± 0.23	20	3
SEQ ID NO:23	AcF-[X <sup>2</sup> PdChaWR]	4.77 ± 0.14*	17	3	6.09 ± 0.08*	0.8	4
SEQ ID NO:11	AcF-[OPdChaWR]	4.60 ± 0.06*	16	4	6.42 ± 0.10	0.4	4
SEQ ID NO:24	AcKF-[OPdChaWR]	4.96 ± 0.03	11	3	6.73	0.2	1

Table 6 (cont.)

SEQ. ID NO:	PEPTIDE	pD <sub>2</sub> ± Se <sup>a</sup>	IC <sub>50</sub> (μM) <sup>a</sup>	(n)	pD <sub>2</sub> ± SE <sup>b</sup>	IC <sub>50</sub> (μM) <sup>b</sup>	(n)
SEQ. ID NO: 14	F-[XPdChaWR]	4.39 ± 0.10*	41	3	nd		
SEQ. ID NO: 16	F-[X <sup>2</sup> PdChaWR]	5.42 ± 0.05	3.8	3	6.70 ± 0.04	0.4	3
SEQ. ID NO: 25	F-[OPdChaWR]	5.51 ± 0.07	3.1	3	5.79 ± 0.34*	1.6	3
SEQ. ID NO: 26	F-[KPdChaWR]	5.09 ± 0.08	8.1	3	5.55 ± 0.57*	2.8	3
Effect of L-Arg on antagonist binding affinity and antagonist potency							
SEQ. ID NO: 17	AcF-[OPdChaWR]	6.57 ± 0.05*	0.3	3	7.91 ± 0.17*	0.01	3
SEQ. ID NO: 13	F-[XPdChaWR]	4.98 ± 0.05	10	3	5.63 ± 0.13*	2.4	3
SEQ. ID NO: 15	F-[X <sup>2</sup> PdChaWR]	6.50 ± 0.04*	0.3	5	7.36 ± 0.13	0.04	3
SEQ. ID NO: 27	F-[OPdChaWR]	7.21 ± 0.01*	0.06	3	7.41 ± 0.14	0.04	3
SEQ. ID NO: 28	F-[KPdChaWR]	6.50 ± 0.12*	0.3	4	6.69 ± 0.04	0.2	3